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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/518,302	05/31/2005	Pasqua Anna Oreste	GRT/3687-101	7086

23117 7590 12/03/2008

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EXAMINER	
BLAND, LAYLA D	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
12/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,302	ORESTE ET AL.	
	Examiner	Art Unit	
	LAYLA BLAND	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-134* is/are pending in the application.

4a) Of the above claim(s) *71-89,110-131 and 134* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *90-109 and 132-133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group II, claims 90-109 and 132-33 and amendment of claim 71 in the reply filed on September 16, 2008 is acknowledged. The traversal is on the ground(s) that Groups I and II have unity of invention because the cited reference does not teach products having a degree of sulfation of at least 4. Applicant's argument is not persuasive because MPEP 1850 states that "a process is specially adapted for the manufacture of a product if it inherently results in the product." Oreste et al. (US 2002/0062019, of record) teaches a process wherein an epiK5-N-sulfate derivative is kept in a neutral solution with tetrabutylammonium hydroxide to obtain the ammoniam salt of the polysaccharide, which is then freeze dried and subjected to oversulfation [0070] and N-sulfated [0085]. This process, which is the same as the process of claim 71, results in a product having a degree of sulfation from 2.3 to 2.9, as was noted by Applicant in the response dated September 16, 2008. Thus, the claimed process does not inherently result in the claimed product which has a degree of sulfation of at least 4.0. Applicant further traverses on the ground that Groups I-IV are closely linked to each other by a "starting material-intermediate-final product" relationship. MPEP 1850 states that unity of invention shall be considered to be present in the context of intermediate and final products when the intermediate and final products have the same essential structural element. Group I is drawn to an epiK5-N,O-oversulfate (N and O are sulfated), Group III is drawn to an epiK5-amine-O-oversulfate derivative (N is not sulfated, O is sulfated), and Group IV is drawn to a LMW epiK5-N-sulfate (only N is sulfated). Groups III and IV are not seen to have the same

essential structural element as Group I because the activity of the compounds of Group I relies upon the presence of N-sulfates and O-sulfates and both are considered essential structural elements. Furthermore, the only common structural element between all three groups is simply a glycosaminoglycan, which is neither novel nor non-obvious. It is further noted that MPEP 1850 states, regarding “more extensive combinations" than product, process of manufacture and use; or process and apparatus; or product, process of manufacture and apparatus should be looked at carefully and that the proliferation of claims arising from a combined effect of this kind should be accepted only exceptionally. In the instant case there are three different products and two different processes for the manufacturing of these.

The requirement is still deemed proper and is therefore made FINAL.

Claims 71-89, 110-131 and 134 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on September 16, 2008.

Claims 71-134 are pending. Claims 71-89, 110-131 and 134 are withdrawn from consideration. Claims 90-109, 132, and 133 are pending and are examined on the merits herein.

This application claims foreign priority to Italian Applications No. MI2002A001345, filed June 18, 2002, MI2002A001346, filed June 18, 2002, and MI2002A001854, filed August 27, 2002 under 35 U.S.C. 119(a)-(d). The certified copy of the priority has been filed with the instant Application. It is noted that the Italian

priority applications are in Italian; no translation of said Italian applications into English has been provided.

Claim Objections

Claim 94 is objected to because of the following informalities: glucosamine is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 90-109 and 132-133 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 90 (and dependent claims) recites the limitation "sulfation degree of at least 4." The specification, page 7, defines "epiK5-N,O-oversulfate" as completely N-sulfated with a sulfation degree of at least 4. Thus, it is clear that the product is completely N-sulfated but it is unclear where and in what quantity the other positions of the product are sulfated in order to reach a sulfation degree of at least 4. The claim is also unclear because the maximum degree of sulfation is unclear; no upper limit is recited. The skilled artisan would not be apprised of the structure of the claimed product.

Claim 90 (and dependent claims) recites the limitation “basically inactive for coagulation.” The specification does not define “inactive for coagulation” or “basically” and the skilled artisan would not be aware of which compounds meet the limitation and which do not. It is further noted that “basic” has more than one meaning; it can refer to chemical basicity or can be used as a synonym for “essential.” Claim 90 is drawn to a chemical compound and the use of "basic" adds ambiguity.

Claim 94 refers to glucuronic units, iduronic units, and "remaining uronic units." It is unclear what the remaining uronic units are, if they are other than glucuronic or iduronic units.

Claim 103 (and dependent claims) is drawn to a LMW-epiK5-N,O-oversulfate having a mean molecular weight from approximately 2,000 to approximately 16,000. The specification, page 7, states that LMW means "from approximately 1,500 to approximately 12,000." The limitations of claim 103 fall outside the definition of LMW given in the specification. Thus, the meaning of “LMW” is unclear.

Claim 106 is drawn to a LMW-epiK5-N,O-oversulfate according to claim 101, in which the uronic units are 20-60% consisting of iduronic acid. Claim 101 requires an iduronic acid content of 50-55%. Thus it is unclear whether there is an error in the claims.

Claim 107 ultimately depends from claim 98 and recites formula III’b. Formula III’b contains moieties which fall outside of the definition in claim 98.

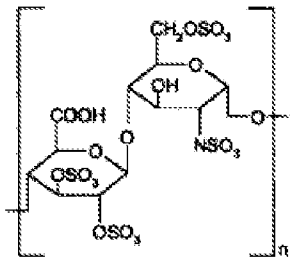
Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 90, 91, 93, and 132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leali et al. (The Journal of Biological Chemistry, Vol. 276, No. 41, Issue of October 12, pp. 37900-37908, 2001).

Leali et al. teach highly N,O-sulfated K5 polysaccharide derivatives [see abstract and Figure 1, shown below]. The degree of sulfation was 3.84 and the molecular weight was 15,000 [Table I]. The degree of sulfation modulates the biological activity of sulfated K5 derivatives. N-sulfation is a requirement for angiostatic activity of K5 derivatives that must also be sulfated in O positions [page 37907, first column, last paragraph]. The products were prepared in the presence of sodium hydroxide and sodium carbonate [page 37901, Experimental Procedures], which would be expected to give the sodium salt. The highly N,O-sulfated K5 derivative exerts a potent FGF2 antagonist and angiostatic activity and has low anticoagulant activity, which makes them attractive targets for design of novel therapeutic compounds [page 37907, last paragraph]. The instant specification states that by “epiK5” is meant the K5 and its derivatives. Thus, the definition of epiK5 does not require an epimerized product.



K5-N,OS(H)

Leali's product differs from the claimed product in that the degree of sulfation is 3.84 as compared to the claimed "at least 4."

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare Leali's product with greater degree of sulfation. 3.84 is very close to 4, and Leali teaches that the more sulfated product had desired characteristics compared to the less sulfated products. Thus, the skilled artisan would be motivated to prepare a product with greater degree of sulfation. Leali suggests the use of the product for therapeutic purposes, so a pharmaceutical composition is also obvious.

As MPEP 2144.05 states "a prima facie case of obviousness exists where the claimed ranges and prior art ranges do not overlap but are close enough that one skilled in the art would have expected them to have the same properties. Titanium Metals Corp. of America v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (Court held as proper a rejection of a claim directed to an alloy of "having 0.8% nickel, 0.3% molybdenum, up to 0.1% iron, balance titanium" as obviousover a reference disclosing alloys of 0.75% nickel, 0.25% molybdenum, balance titanium and 0.94% nickel, 0.31% molybdenum, balance titanium.)."

Therefore the claims are seen to be obvious over the prior art teachings.

Claims 90-109 and 132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casu et al. (WO 98/42754, October 1, 1998) in view of Leali et al. (The Journal of Biological Chemistry, Vol. 276, No. 41, Issue of October 12, pp. 37900-37908, 2001).

Casu et al. teach products prepared from either K5 polysaccharide or epimerized K5 polysacharide [page 10, lines 1-8]. The products have a sulfate/carboxyls molar ratio from 2.0 to 3.5 and molecular weight of 1,500-8,000 or 8,000 to 18,000, or 8,000 to 25,000 [claims 1-5]. The epimerized products are 30:70 or 60:30 iduronic acid to glucuronic acid [page 10, lines 5-7]. The products are prepared using sodium acetate [page 11, part d], which would be expected to give the sodium salt. Casu also teaches that low molecular weight heparins have lower anticoagulant activity and better bioavailability compared to traditional heparins [page 2, lines 10-21]. Supersulfated glycosaminoglycans can be prepared by methods known in the art [page 4, lines 15-18].

Casu et al. do not teach products having a sulfation degree of greater than 3.5.

Leali et al. teach as set forth above, that oversulfated K5 products have low coagulant activity.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare highly sulfated products from epimerized or non-epimerized K5, as taught by Casu, with a high degree of sulfation in order to obtain a product with low coagulant activity as taught by Leali. Casu teaches that either can be

used to prepare biologically active supersulfated glycosaminoglycans which are similar to heparin. Since Leali teaches the desirability of a product which has low anticoagulant activity, the skilled artisan could envision using low molecular weight products and highly sulfated products.

Claims 90-109 and 132-133 are rejected under 35 U.S.C. 103(a) as being unpatentable over Casu et al. in view of Leali et al. as applied to claims 90-109 and 132 above, and further in view of Oreste et al. (US 2002/0062019, May 23, 2002, of record).

Casu and Leali teach as set forth above. Casu and Leali do not teach a cosmetic composition.

Oreste et al. teaches glycosaminoglycans derived from epimerized K5 polysaccharides which have been subjected to O-oversulfation and N-sulfation [see abstract]. An additional N-sulfation step is required because some N-sulfate groups are lost during O-oversulfation [0120]. In one example, the molecular weight is 7,000 and about 55% of the uronic acid units are those of iduronic acid [claim 44]. Sodium or calcium salts are taught [claim 46]. Topical compositions comprising carriers such as gels, creams, or lotions are taught [0185]. These could be considered cosmetic compositions.

It would have been obvious to one of ordinary skill in the art to prepare a cosmetic composition comprising the derivatives as discussed above. Leali, Casu, and Oreste all teach glycosaminoglycans prepared from K5 polysaccharide, which are O-sulfated and N-sulfated. Oreste teaches that these can be used in a topical composition

with lotions or creams, so it would have been obvious to prepare the same type of composition using the derivatives as discussed above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 90-109 and 132-133 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of U.S. Patent No. 7,268,122 in view of Casu et al. (WO 98/42754, October 1, 1998). The claims of U.S. Patent No. 7,268,122 are drawn to the use of a N,O oversulfated K5 polysaccharide having a sulfation degree of 3.2 to 4. The claims of U.S. Patent No. 7,268,122 do not teach the use of an epimerized K5 polysaccharide. However, Casu teaches as set forth above, that the epimerized and non-epimerized K5 polysaccharide

can be used interchangeably. Thus, the instant claims are obvious over the claims of U.S. Patent No. 7,268,122 in view of Casu.

Claims 90-109 and 132-133 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-27 of U.S. Patent No. 6,992,183 in view of Casu et al. (WO 98/42754, October 1, 1998). The claims of U.S. Patent No. 6,992,183 are drawn to a N,O oversulfated K5 polysaccharide having a sulfation degree of 3.2 to 4 and use thereof. The claims of U.S. Patent No. 6,992,183 do not teach the use of an epimerized K5 polysaccharide. However, Casu teaches as set forth above, that the epimerized and non-epimerized K5 polysaccharide can be used interchangeably. Thus, the instant claims are obvious over the claims of U.S. Patent No. 6,992,183 in view of Casu.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAYLA BLAND whose telephone number is (571)272-9572. The examiner can normally be reached on Monday - Friday, 7:00 - 3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anna Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Layla Bland/
Examiner, Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner
Art Unit 1623